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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/732,919	12/10/2003	David J. Yang	UTSC:841US	7351

32425 7590 11/05/2007

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
11/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/732,919	YANG ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,10-28,31-51 and 60* is/are pending in the application.

4a) Of the above claim(s) *5,10-28 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,31-33, 35-51 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 8/27/2007, in reply to the Notice of Non-Responsive Amendment mailed 8/3/2007, is acknowledged and has been entered. The Response filed 3/30/2007, in reply to the Office Action mailed 1/4/2007 is also acknowledged. Per the Response filed 8/27/2007, claims 1, 2, 5, 10 and 11 have been amended. Claims 3, 4, 6 – 9, 29, 30 and 52 – 59 have been cancelled. New claim 60 has been added. Claims 1, 2, 5, 10 – 28, 31 – 51 and 60 are pending, of which claims 5, 10 – 28 and 34 are withdrawn from consideration at this time. Claims 1, 2, 31 – 33, 35 – 51 and 60 are readable upon the elected invention and are examined herein on the merits for patentability.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 2/14/2007 was filed after the mailing date of the Office Action mailed on 1/4/2007. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

Applicant's arguments, filed 3/30/2007, with respect to the rejection of claims 1, 2, 6, 7, 31 – 33 and 35 – 51 under 35 U.S.C. 101 as claiming the same invention as

claims 1, 2, 5, 6, 27 – 29 and 31 – 47 of copending application No. 10/703,405 have been fully considered. The rejection has been WITHDRAWN as being overcome in view of the cancellation of the '405 application.

Applicant's arguments, filed 3/30/2007, with respect to the rejection of claims 1, 2 and 31 – 33 and 35 – 51 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 5 of US 6,692,724 have been fully considered but they are not persuasive for reasons set forth hereinbelow. The rejection has been MAINTAINED.

Applicant's arguments, filed 3/30/2007, with respect to the rejection of claims 35 – 41 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 5 and 7 of US 7,067,111 have been fully considered but they are not persuasive for reasons set forth hereinbelow. The rejection has been MAINTAINED.

Applicant's arguments, filed 3/30/2007, with respect to the rejection of claims 38 on the ground of provisional nonstatutory obviousness-type double patenting as being unpatentable over claims 52 – 73 of copending application No. 10/672,763 have been fully considered but they are not persuasive for reasons set forth hereinbelow. The rejection has been MAINTAINED.

Applicant's arguments, filed 3/30/2007, with respect to the rejection of claims 42 – 51 on the ground of provisional nonstatutory obviousness-type double patenting as being unpatentable over claims 42 – 50 and 74 – 81 of copending application No. 11/405,334 have been fully considered but they are not persuasive for reasons set forth hereinbelow. The rejection has been MAINTAINED.

Applicant's arguments, filed 3/30/2007, with respect to the rejection of claims 1, 2, 6, 31-33 and 35 – 51 under 35 U.S.C. 112, first paragraph, have been fully considered. The rejection has been WITHDRAWN as being overcome by amendment.

Applicant's arguments, filed 3/30/2007, with respect to the rejection of claims 1, 2, 6, 31-33 and 35 – 51 under 35 U.S.C. 112, second paragraph, have been fully considered. The rejection has been WITHDRAWN as being overcome by amendment.

Applicant's arguments, filed 3/30/2007, with respect to the rejection of claims 1, 2, 31-33 and 35 – 51 under 35 U.S.C. 102(b) as being anticipated by Yang *et al.* (WO 01/91807), have been fully considered. The rejection has been WITHDRAWN as being overcome by amendment.

Applicant's arguments, filed 3/30/2007, with respect to the rejection of claims 1, 2, 6, 7, 31 – 33 and 35 – 51 under 35 U.S.C. 103(a) as being unpatentable over Iyer *et al.* (*J. Nucl. Med.*, 2001, 42, p. 96 – 104) in view of Yang *et al.* (WO 01/91807), have

been fully considered but they are not persuasive for reasons set forth hereinbelow.

The rejection has been MAINTAINED.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The double patenting rejections cited above are MAINTAINED for reasons set forth in the Office Action mailed 1/4/2007. Applicant argues on pages 10 – 11 of the Response filed 3/30/2007 that in view of the amendment, none of the targeting ligands are of overlapping scope with those set forth in the cited patents or applications.

This is found non-persuasive because while the ligands which were formerly identical in scope have been removed from the claims, further examples of targeting ligands which are overlapping in scope remain pending. An example of ligands which

are overlapping in scope include herceptin, as in the instant application, and "anticancer agents," which are recited in the '724 or '111 patents, or the '763 or '919 applications, for example.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 31 – 33 and 35 – 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer *et al.* (*J. Nucl. Med.*, 2001, 42, p. 96 – 104) in view of Yang *et al.* (WO 01/91807), for reasons set forth in the Office Action mailed 1/4/2007.

Applicant argues on page 14 of the Response filed 3/30/2007 that "the cited combination of references fails to teach or suggest those tissue specific ligands set forth in the presently pending claims." Applicant argues that Iyer has been cited as teaching or suggesting penciclovir as a targeting ligand, and that none of the claims as written pertain to penciclovir as a targeting ligand. Applicant argues that one of ordinary skill in the art would not be motivated to provide any of the claimed compounds based on the combined teachings of Iyer and Yang.

This is non-persuasive because while penciclovir, or aminopenciclovir, was not listed as a specific targeting ligand that was claimed as of the amendment filed 3/30/2007 (i.e. the term "disease cell cycle targeting compound" was removed from claim 1, and claim 7, wherein the ligand is aminopenciclovir, was cancelled in the

amendment filed 3/30/2007); the reintroduction of aminopenciclovir into claims 1 and 2 via the amendment filed 8/27/2007 appears to render the argument of the 3/30/2007 Response that "the cited combination of references fails to teach or suggest those tissue specific ligands set forth in the presently pending claims" moot. This is because aminopenciclovir is indeed a tissue specific ligand set forth in the claims now presently pending. No arguments were presented in the Response filed 8/27/2007 which clearly point out the patentable novelty which Applicant thinks the claims present in view of the state of the art disclosed by the references cited made. Further, they do not show how the amendments avoid such references or objections.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to use **penciclovir as a targeting agent for tissue-specific imaging** because Iyer specifically teaches the use of ^{18}F radiolabled penciclovir (i.e. 8-[^{18}F]fluoropenciclovir (FPCV)) as a tissue-specific reporter in PET imaging. It would have been obvious to substitute the ^{18}F radionuclide of the reporter with another radionuclide, such as a ^{99m}Tc radionuclide in the form of an N_2S_2 chelate, because Yang teaches the benefits of conjugating a variety of targets to such chelates for tissue specific PET imaging. Both Iyer and Yang demonstrate targeted tissue-specific PET imaging, and Yang teaches that conjugation of a wide variety of targeting agents for tissue specific PET imaging is well-known in the imaging arts. Specific targeting agents taught by Yang may include acyclovir and ganciclovir, for example (page 4, line 17). Penciclovir differs in structure only by one atom from ganciclovir (see position X, Figure 1 in Iyer). Radiolabled penciclovir and ganciclovir were both taught

by Iyer to be HSV1-tk gene expression reporters. One would have been motivated to substitute penciclovir for ganciclovir in the N_2S_2-targeting ligand conjugates and would have had a reasonable expectation of success in doing so because Iyer specifically teaches that radiolabled penciclovir is a better reporter probe for imaging lower levels of HSV1-tk gene expression than radiolabled ganciclovir (abstract). Furthermore, one would have been motivated to **modify penciclovir with an amino group in order to be conjugated to the chelate** because Yang teaches that the targeting ligands for use in conjugation should possess either amino or hydroxy groups that are able to conjugate to the N_2S_2 chelate on either one or both acid arms. If amino or hydroxy groups are not available, a desired ligand may still be conjugated to EC and labeled with ^{99m}Tc using the methods of the invention by adding a linker (page 19, lines 1 – 5). An example of the modification of targeting agents with amino groups (for the case of folic acid as the targeting ligand, for example) for the purpose of conjugation of the target to the acid group of an N_2S_2 chelate via an amide bond is specifically shown in Figure 1 of Yang.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 60 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to the compound of claim 6, wherein the

targeting ligand is adenosine, aminopenciclovir, FIAU, FIRU, IVFRU, GCV, PCV, FGCV, FPCV, FHPG, FHBG or guanine. However, claim 6 is a cancelled claim and thus the dependent claim 60 is unclear regarding the nature of the compound. As such, the metes and bounds of the claims are not clearly set forth and the scope of the invention cannot be distinctly ascertained. For the purposes of search, it is interpreted that the claim was intended to be dependent upon either one of claims 1 or 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer *et al.* (*J. Nucl. Med.*, 2001, 42, p. 96 – 104) in view of Yang *et al.* (WO 01/91807).

Iyer discloses ^{18}F radiolabled penciclovir as a reporter probe for imaging HSV1-tk gene expression using PET. The herpes simplex virus type 1 thymidine kinase reporter gene has been studied with various reporter probes, and Iyer introduces penciclovir as a reporter probe for PET imaging studies (page 96). Structurally similar acyclovir and ganciclovir have been used as antiviral agents, and penciclovir is also a highly selective antiherpes viral agent (page 97). Both ganciclovir and penciclovir have been modified with an ^{18}F radionuclide at position 8 of the side chain to yield 8-[^{18}F]Fluoroganciclovir and 8-[^{18}F]Fluoropenciclovir respecitively (Figure 1), and were used as site-specific reporter probes for imaging purposes.

Iyer fails to specifically teach that penciclovir is conjugated to an N_2S_2 moiety chelated to a radionuclide.

Yang discloses ethylenedicysteine (EC)-drug conjugates, compositions, and methods for tissue specific disease imaging as set forth above. The imaging compositions include a radionuclide label chelated with ethylenedicysteine and a tissue-specific ligand on one or both of its acid arms (i.e. R_9 and/or R_{10} may be carboxylic acid or may be covalently bound to a targeting ligand). The tissue specific ligand is a compound that, when introduced to a body will specifically bind to a specific type of tissue as set forth above.

Yang fails to specifically teach that the targeting ligand is aminopenciclovir.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use penciclovir as a targeting agent for tissue-specific imaging because Iyer specifically teaches the use of ^{18}F radiolabled penciclovir (i.e. 8-

[^{18}F]fluoropenciclovir (FPCV)) as a tissue-specific reporter in PET imaging. It would have been obvious to substitute the ^{18}F radionuclide of the reporter with another radionuclide, such as a ^{99m}Tc radionuclide in the form of an N_2S_2 chelate, because Yang teaches the benefits of conjugating a variety of targets to such chelates for tissue specific PET imaging. Both Iyer and Yang demonstrate targeted tissue-specific PET imaging, and Yang teaches that conjugation of a wide variety of targeting agents for tissue specific PET imaging is well-known in the imaging arts. Specific targeting agents taught by Yang may include acyclovir and ganciclovir, for example (page 4, line 17). Penciclovir differs in structure only by one atom from ganciclovir (see position X, Figure 1 in Iyer). Radiolabled penciclovir and ganciclovir were both taught by Iyer to be HSV1-tk gene expression reporters. One would have been motivated to substitute penciclovir for ganciclovir in the N_2S_2-targeting ligand conjugates and would have had a reasonable expectation of success in doing so because Iyer specifically teaches that radiolabled penciclovir is a better reporter probe for imaging lower levels of HSV1-tk gene expression than radiolabled ganciclovir (abstract). Furthermore, one would have been motivated to modify penciclovir with an amino group (i.e. aminopenciclovir) in order to be conjugated to the chelate because Yang teaches that the targeting ligands for use in conjugation should possess either amino or hydroxy groups that are able to conjugate to the N_2S_2 chelate on either one or both acid arms. If amino or hydroxy groups are not available, a desired ligand may still be conjugated to EC and labeled with ^{99m}Tc using the methods of the invention by adding a linker (page 19, lines 1 – 5). An example of the modification of targeting agents with amino groups (for the case of folic acid as the

targeting ligand, for example) for the purpose of conjugation of the target to the acid group of an N_2S_2 chelate via an amide bond is specifically shown in Figure 1 of Yang.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER